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Chromosome Segregation: Monopolin Goes Spindle

At anaphase onset the mitotic spindle undergoes dramatic changes in order to segregate sister chromatids. Surprisingly, the monopolin complex, best known for its role at kinetochores in meiosis, is now shown to localize to, and stabilize, the mitotic anaphase spindle.

Anton Khmelinskii and Elmar Schiebel*

During meiosis, a single round of DNA replication is followed by two rounds of cell division (meiosis I and II), resulting in four daughter cells with half the chromosomes. Meiosis I is characterized by segregation of homologous chromosomes in a process known as reductional division and requires the attachment of sister kinetochores to microtubules organized by the same spindle pole. In the budding yeast *Saccharomyces cerevisiae*, a single microtubule contacts the pair of sister kinetochores in meiosis I [1], and the meiosis-specific monopolin-complex component Mam1 is essential for this mono-orientation of sister kinetochores [2] (Figure 1A). Mam1 forms a complex together with the casein-kinase-1 Hrr25 and the ubiquitous nucleolar proteins Csm1 and Lrs4 [3,4]. In the fission yeast *Schizzosacharomyces pombe*, kinetochores bind multiple microtubules, as in animal cells, and a monopolin complex comprising Pcs1 and Mde4 (orthologs of budding yeast Csm1 and Lrs4, respectively) prevents attachment of microtubules emanating from opposite poles to the same kinetochore (merotelic attachments) in mitosis and meiosis II [5] (Figure 1B). In an unexpected twist, Choi *et al.* [6] now report in this issue of *Current Biology* that the fission yeast monopolin complex is targeted by a Cdc14-like phosphatase [7,8] to the anaphase spindle where it contributes to spindle elongation and stabilization.

At the metaphase to anaphase transition of mitosis, remarkable changes in spindle morphology and dynamics take place. During metaphase, microtubules display high turnover, which favours kinetochore capture by kinetochore microtubules (kMTs). This increase in microtubule dynamics is promoted by the activity of the cyclin-dependent kinase Cdk1 [9,10]. Once all sister chromatids are attached to kMTs from opposite spindle poles (bioriented), the protease separase is activated. Separase dissolves sister chromatid cohesion, thus allowing shrinking kMTs to move the chromosomes towards the spindle poles, and cells advance into anaphase. Suddenly microtubules are stabilized, and the spindle midzone is formed by overlapping interpolar microtubules (iMTs) in the middle of the spindle where microtubule-bundling proteins, kinesin motor proteins and signalling molecules localize. Sliding forces produced by motor proteins of the midzone drive spindle elongation, separating the sister chromatids further apart [11,12].

In budding and fission yeast, anaphase spindle elongation is particularly drastic (as much as five fold), largely contributing to the physical separation of sister chromatids. Cdc14 is an important regulator of the anaphase spindle. Decreasing Cdk1 activity and increasing Cdc14 phosphatase activity trigger a program of dephosphorylation of Cdk1 targets that guides cells through anaphase and eventually to the G1 phase of the cell cycle (mitotic exit) [13,14]. In a Cdc14-dependent manner, several microtubule-associated proteins are recruited to or regulated at the anaphase spindle to modulate microtubule behaviour. Assembly of the spindle midzone is directly triggered by the Cdc14-dependent dephosphorylation of the microtubule-bundler Ase1 [15]. Dephosphorylation of the DASH complex component Ask1 by Cdc14 is responsible for the reduced dynamics of iMTs in anaphase [10]. Regulation of the ortholog of the inner centromere protein (INCENP) Sli15 by Cdc14 targets the Aurora B chromosomal passenger complex to the anaphase spindle where it controls spindle stability [16].

The fission yeast Cdc14 homolog, Clp1 (also known as Flp1), also interacts with Aurora B kinase [17], suggesting that functions of Cdc14-like phosphatases are conserved between budding and fission yeast. Choi *et al.* [6] now identify the first Clp1 target involved in regulation of the anaphase spindle. They show that the fission yeast monopolin complex, which is entrapped in the nucleolus during interphase, becomes released as cells enter mitosis. Mde4 and Pcs1, as mentioned above, bind to kinetochores to ensure chromosome biorientation. Upon Clp1-dependent dephosphorylation of Cdk1 sites on Mde4, the monopolin complex localizes to the extending anaphase spindle. Surprisingly, Pcs1–Mde4 does not uniformly decorate the anaphase spindle as is the case, for example, for the DASH complex [18]. Instead, the monopolin complex seems to be excluded from the spindle midzone, a region of overlapping antiparallel iMTs. Whether the monopolin complex indeed binds preferentially to parallel microtubules, as suggested by Choi *et al.* [6], awaits experimental confirmation. Initial *in vitro* microtubule-binding experiments with recombinant Pcs1–Mde4 complex did not show microtubule-binding activity. Thus, it is presently unclear

how the monopolin complex prevents spindle collapse, which is otherwise observed in cells lacking spindle-associated Pcs1–Mde4. It will also be important to understand whether the spindle-stabilizing function of the monopolin complex reported in fission yeast is conserved.

The finding that Pcs1–Mde4 stabilizes the spindle in anaphase [6] expands the increasing list of functions of the monopolin complex. Besides its role at kinetochores, the budding yeast Csm1–Lrs4 monopolin complex was shown to interact with the RENT complex (regulator of nucleolar silencing and telophase exiting; consisting of Net1, Sir2 and Cdc14 phosphatase) in the nucleolus where the monopolin complex suppresses unequal recombination of ribosomal DNA (rDNA) repeats. The recruitment of condensin to specific rDNA regions by Csm1–Lrs4 may be the underlying mechanism of this suppression [19]. In addition, the Csm1–Lrs4 complex tethers rDNA to the nuclear envelope through binding to two proteins of the inner nuclear membrane, the Heh1 and Nur1 proteins [20] (Figure 1C). In light of the finding by Choi *et al.* [6], it will be interesting to see whether these functions of the budding yeast monopolin complex are regulated by Cdc14 phosphatase.

How does the monopolin complex fulfil these diverse functions? An interesting concept put forward by K. Nasmyth is a clamp-like function of the monopolin complex [3] (Figure 1A). In this model, Pcs1- and Csm1-containing complexes clamp adjacent microtubule-binding sites of kinetochores together so that they interact only with microtubules emanating from the same spindle pole. The role of the monopolin complex in rDNA tethering to the nuclear envelope is consistent with a crosslinking molecule that connects the rDNA repeats with proteins of the inner nuclear membrane [20] (Figure 1C). Crosslinking may also be the function of the fission yeast monopolin complex at the anaphase spindle, although it is presently unclear which microtubule-binding protein would be crosslinked and why Pcs1–Mde4 is not found at the iMTs of the spindle midzone [6] (Figure 1D). Dimerization of monopolin complex subunits [6] may help to join homotypic anchor proteins at microtubule-attachment sites of kinetochores, parallel microtubules or rDNA repeats. *In vitro* studies with purified monopolin components and structural data are needed to unravel the molecular mechanism of this chameleon complex.

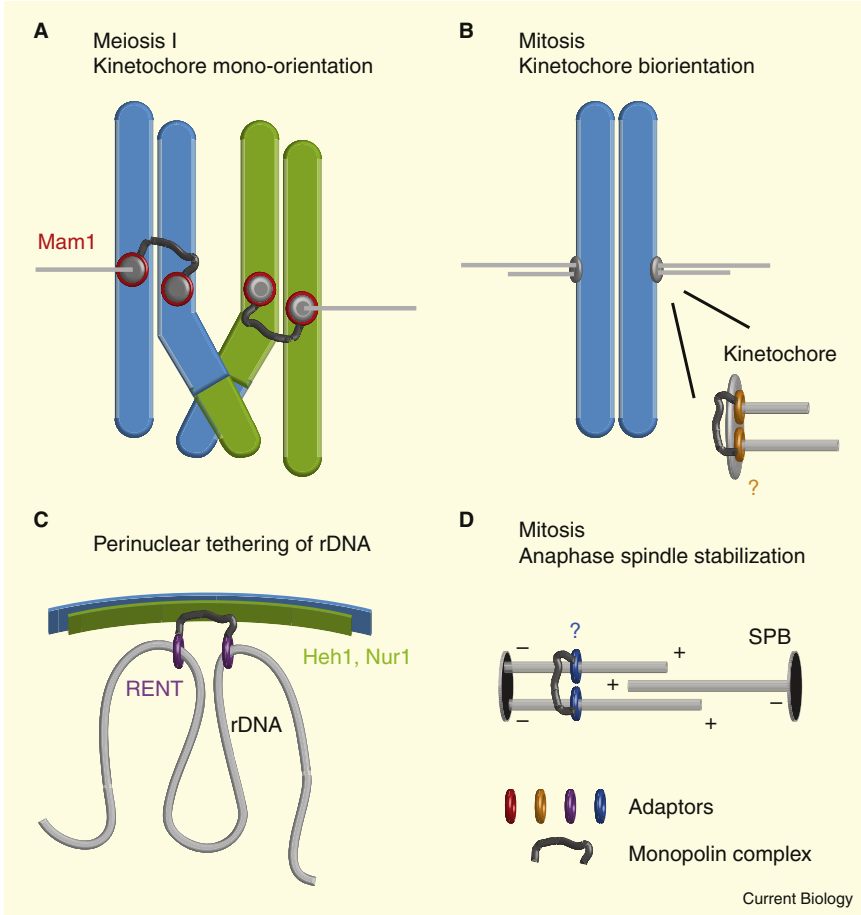

Figure 1. Monopolin complex functions.

Depicted here is a model for the function of the monopolin complex in (A) kinetochore mono-orientation in budding yeast meiosis I [3], (B) kinetochore biorientation in fission yeast mitosis and meiosis II [5], (C) rDNA tethering to the nuclear envelope in budding yeast [20] and (D) stabilization of the mitotic anaphase spindle in fission yeast [6]. Note that 'monopolin complex' refers to Csm1–Lrs4 in budding yeast and Pcs1–Mde4 in fission yeast. In the case of (A), Mam1 may function as an adaptor at kinetochores for the Csm1–Lrs4 monopolin complex, although binding of Mam1 to kinetochores also requires Csm1–Lrs4 [3]. The RENT complex may provide such a function for the tethering of rDNA to the nuclear envelope [20]. How the monopolin complex is bound to microtubules is presently unclear [6]. The adaptors are depicted as rings in all panels for simplicity.

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Learning and Memory: While You Rest, Your Brain Keeps Working

A recent study shows that brain activity recorded while the human subject is at 'rest' is significantly affected by a prior learning episode. These results suggest that understanding resting brain activity may be critical to understanding how humans learn from experience.

Justin L. Vincent[1,2]

On average, the brain uses approximately a fifth of the energy consumed by the body, of which the vast majority is directly related to spontaneous neuronal signaling (for review see [1]). Most of this ongoing spontaneous brain activity is not random; it is correlated from the level of individual neurons [2] all the way up to widely distributed functional brain systems [3]. Functional magnetic resonance imaging (fMRI) studies in humans have shown that the blood-oxygen-level dependent (BOLD) signal — which is thought to reflect neural activity — is correlated within multiple distributed brain networks that closely correspond to the brain networks commonly activated during task performance. This correlated spontaneous brain activity is thought to reflect 'functional connectivity' within brain networks (for review see [4]). But despite the fact that most of the brain's energy budget is devoted to maintaining highly organized patterns of coherent spontaneous activity, very little is known about the functional role of these spontaneous fluctuations. It has been previously suggested that these spontaneous activity patterns may consolidate the past, stabilize brain ensembles, and prepare us for the future [5,6]. Until recently, however, there has been little evidence to support this view.

A study reported in this issue of *Current Biology* by Albert *et al.* [7] sheds new light on the role of spontaneous activity by demonstrating that a motor learning episode significantly modulated spontaneous BOLD fluctuations recorded during the *rest period* that followed the learning episode. The authors first recorded spontaneous signals in the brains of human participants while they rested, and found functional connectivity within two distinct brain networks that included regions in the cerebellum or in frontal and parietal cortex (Figure 1, left panel). These frontal, parietal, and cerebellar regions are typically engaged during motor learning (for example [8–10]). Then, the participants learned a complex task that involved hand–eye coordination and the learning of a novel motor skill (Figure 1, middle panel). Several minutes after the participants had learned the new task, the authors again recorded resting brain activity within the cerebellar and frontal-parietal networks: they found that spontaneous BOLD fluctuations in these networks were more synchronized following learning (Figure 1, right panel). Further, these learning-related changes in brain functional connectivity were not limited to the time immediately following learning because the subjects performed a different, unrelated task between the learning episode and the final recorded rest period. Importantly, the authors showed that performance of a similar task that did not require learning a new skill did not result in any significant changes in the functional connectivity of the frontal-parietal network or cerebellar network. The implication is that motor learning, but not motor performance, increased the strength of subsequently recorded functional connectivity. These results suggest that newly formed memories leave a 'trace' that can be measured by examining spontaneous activity recorded during rest periods.

Learning to perform a complex motor task, such as playing a guitar, may be difficult initially. Once learned, however, the ability to perform that task becomes more automatic and can remain within one's memory for years. This process of stabilizing a long-term memory is referred to as consolidation. It has long been thought that sleep plays a critical role in consolidation by reinforcing significant synaptic connections and eliminating accidental connections. The principle findings that linked sleep with learning were the correlation between the amount of time spent in rapid-eye-movement sleep